REMARKS/ARGUMENTS

Reconsideration of the above-identified application respectfully requested.

In light of the Examiner's Advisory Action mailed July 21, 2003, and subsequent telephonic communications between the Examiner the undersigned on August 4, 2003, the independent claims were recast as product-by-process claims.

Applicants submit herewith Amendments that heed the Examiner's specific advice. The Examiner maintained a rejection of record on September 8, 2003, suggesting that in the interview "adding the specific step of ultracentrifugation to the product-by-process claim would render the claims allowable." Taking into account the language of the specification and the Examiner's suggestion, claims 1 and 57 have been amended to include the step of "purifying a factor by ultrafiltration of said supernatant." There is support in the specification for such language, such as at p. 27, ll. 31-33 and p. 32, ll. 21-34. The specification specifically states at p.74, l. 19-25: "Supernatants were separated into fractions greater and less than 50 kDa by centrifugation at 100 x g for 30 minutes in Millipore Ultrafree Biomax (Bedford, MA) filter devices with nominal 50 kDa limits." Such disclosure is of the process commonly known to those skilled in the art as "ultrafiltration." Ultrafiltration is defined in Dorland's Medical Dictionary (27th ed. Saunders, Philadelphia, 1988) as "filtration through filters with minute pores thus allowing separation of extremely minute particles..." Thus, the claim language includes commonly accepted art terms, supported by the specification, to describe the process claimed by Applicants. The Applicants note that ultrafiltration would not necessarily rely on centrifugation or ultracentrifugation, but could similarly be accomplished by means of pressure or vacuum. Thus, no new matter is added by this amendment and entry of the amendment is respectfully requested. Accordingly, Applicants assert that no claims have been narrowed with the meaning of *Festo* (*Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 US 722, 112 S.Ct. 1831, 152 L.Ed.2d 944, 62 USPQ2d 1705 (2002)).

Applicants have made clear in the specification and through the claims under consideration that the instant invention is neither anticipated nor rendered obvious by any prior art, either alone or in combination. Both the specification and the claims make clear that Applicants consider their invention to consist essentially of *only* those components of the cellular supernatant from stimulated cells that are selected by an ultrafiltration membrane with a size exclusion limit of 50 kDa. Those components of the

supernatant of cells stimulated according to the Applicants' invention that are not selected by an ultrafiltration membrane with a size exclusion limit of 50 kDa are excluded from the claimed invention. That the factor may be a multimer based on a monomer of less than 50 kDa size is irrelevant since the active form of the material is greater than 50 kDa in size. Thus, Applicants' claims have also been limited to those components of the cellular supernatant from stimulated cells that do not pass through an ultrafiltration membrane with a size exclusion limit of 50 kDa. The claim language chosen by Applicants, *viz.*, "consisting essentially of", limits the scope of the claims to the specified materials or steps "and those that do not materially affect the basic and novel characteristics" of the claimed invention. *In re Herz*, 537 F.2d 549,551-552, 190 USPQ 461, 463 (CCPA 1976). Applicants, then, believe that the claims make clear that *only* those components from mitogenically stimulated lymphocyte cells of greater than 50 kDa are part of the claimed invention. Thus, the invention is neither anticipated nor rendered obvious by Chang et al.'s fractionation of various components on an SDS-PAGE gel.

The previous Advisory Action stated, *inter alia*, that a "product-by-process claim, which is a product claim that defines the claimed product in terms of the process by which it is made, is proper." Amended claims 1 and 57 now are cast as product-by-process claims that limit the "factor" to one "prepared by purifying a factor by ultrafiltration" of the supernatant to select components having a molecular weight greater than 50 kDa. Fractions of less than 50 kDa in size are detrimental to the function of the 'factor' as shown in Example 1 and Tables 1 and 4A; Example 5, Table 25; and Example 6, Table 27. Each of these tables report data to the effect that the presence of the greater than 50 kDa fraction displays superior results (*e.g.*, anti-viral activity and anti-tumor activity) compared to the less than 50 kDa fraction and greater than the entire supernatant of Triozzi '381.

Thus and contrary to the Examiner's statement, the presence of the components in the less than 50 kDa fraction do have a detrimental affect on the activity of the factor. Inasmuch as Applicants have chosen to exclude such less than 50 kDa fraction, which is their right and which is supported by the data, renders the amended claims patentable. Such results are entirely unexpected in light of the Triozzi '381 reference and cannot have been fathomed from the prior art even with the best of reading of any other prior art.

It is inappropriate to construe the transitional phrase "consisting essentially of" as equivalent to "comprising" in this instance, because those components of the cellular supernatant eliminated by the Applicants' invention by exclusion chromatography clearly do not have a material effect on the basic and novel characteristics of the claimed invention. The specification makes clear that the method of Applicants' invention is superior to the crude preparation disclosed in the art, namely the preparation of the Triozzi in U.S. Patent No. 6,093,381 (Triozzi '381) and Triozzi et al., 1998. Applicants disclose in the specification numerous specific Examples that demonstrate the novel characteristics of their invention. Applicants draw the Examiner's attention in particular to Example 1 and Tables 1 and 4A; Example 5, Table 25; and Example 6, Table 27. Each of these tables report data to the effect that the presence of the greater than 50 kDa fraction displays superior results (*e.g.*, anti-viral activity and anti-tumor activity) compared to the less than 50 kDa fraction and greater than the entire supernatant of Triozzi '381. There can be no doubt that Applicants' invention is a material improvement over the crude preparation of the Triozzi '381 patent. When the claims under consideration are read in light of the specification, Applicants' invention is distinct from, and patentable over, any prior art, alone or in combination.

These data also bespeak of a lack of any double patenting allegations, because there is no way that the skilled artisan could possibly know what material in the crude Triozzi '381 preparation would exhibit superior activity compared to the entire supernatant, much less any certainty that any material therein would exhibit superior activity. Such is unsupported speculation on the part of the Examiner. Moreover, it is possible that fractionation of a supernatant, such as that of Triozzi '381, could destroy all activity.

No prior art either anticipates or makes obvious a factor specifically of greater than 50 kDa, derived from mitogenically stimulated lymphocyte cells, which factor is useful for treating patients afflicted with a disease that leads to an immunosuppressed state. Applicants' claimed factor simply was not in possession of the public prior to the instant invention, and no cited art describes a manner in which the claimed factor could be obtained.

Specific Remarks Regarding Rejections of Record.

Claims 1-8 and 57-66 have been rejected by the Examiner under 35 U.S.C. §102 as being anticipated by Triozzi et al., 1998. Triozzi does indeed disclose subject matter

that is broader than Applicants' invention. Nonetheless, Applicants have made a patentably distinct invention that could not be derived from the disclosure of the Triozzi et al. without extensive experimentation. In fact, there is no certainty that any amount of experimentation would reveal a Factor that would exhibit improved anti-viral and anti-tumor activity compared to the entire supernatant. Again, the Examiner is inherently making this assumption without a whiff of support.

Applicants have disclosed extensive new matter in the instant application that describes the extensive experimentation necessary to enable those skilled in the art to determine that the active components of the supernatant are enriched in that fraction of greater than 50 kDa. The extensive experimentation necessary to make the determination of the relative size of the active factor is *prima facie* evidence that the Applicants' invention is neither anticipated by nor obvious from Triozzi et al.

Claims 1, 5, 57, and 61 have been rejected by the Examiner under 35 U.S.C. §102(b) as being anticipated by Chang *et al.* U.S. Patent No. 4,596,774 (Chang '774). For the same reasons stated above, and in prior responses before the Examiner, Applicants disclosed invention claims matter not disclosed or enabled by the Chang '774 patent. The Chang '774 patent discloses and claims a rather crude method for producing monoclonal antibodies in a cell culture system supplemented with mouse serum. (*See* the only independent claims in Chang '774: Claim 1, col. 11, l. 63; Claim 13 Col. 12, ll. 52-53.) Unlike Chang '774, Applicants preferred embodiment proliferates cells in serum free media. Nor is the method of mitogenic stimulation disclosed by Applicants disclosed by Chang '774. In the instant application, both the specification and the claims make clear that Applicants consider their invention to consist essentially of *only* those components of the cellular supernatant from stimulated cells that are selected by an ultrafiltration membrane with a size exclusion limit of 50 kDa. Applicants' invention is neither disclosed nor enabled by Chang '774, and the Examiner has not specifically cited any disclosure to support such an inference. Therefore Applicants request that the Examiner's rejection be withdrawn.

Claims 1-3 and claims 57-59 have been rejected by the Examiner under 35 U.S.C. §102(b) as being anticipated by Triozzi *et al.* (*Aids Res. and Human Retroviruses*, Vol. 14, No. 8, 1998) (Triozzi *et al.*, 1998). The Examiner does not cite a disclosure in this paper by Triozzi of the characterized fraction that Applicants claim, nor does any such disclosure exist. Those skilled in the art could not identify a particular

fraction that was capable of therapeutic benefit without extensive experimentation. Triozzi *et al.*, 1998 expressly admit lack of knowledge of any therapeutic activity *in vivo*, stating "[n]onetheless, the chemokine-releasing cells expanded in these short-term cultures *ex vivo* may be sufficient to be applied therapeutically as an autologous cellular therapy for HIV-1. The effects of these cells, and whether their infusion can augment a response that is obviously incomplete *in vivo*, are currently under clinical investigation." (Triozzi *et al.*, 1998, p. 648). There is no suggestion of any kind in the Triozzi *et al.*, 1998 citation of any particular size of component of the supernatant that might possibly comprise the active component. The express language of Triozzi *et al.*, 1998 makes clear that the authors do not have any clear and definite idea that the supernatant might be effective for treating patients. The concluding sentences of Triozzi *et al.*, 1998 simply suggest an approach that is obvious to try. There are no identified criteria in Triozzi *et al.*, 1998 that suggest any prediction of the level of experimentation required or of the likelihood of success.

The Examiner has reinstated rejection based on Tanaka et al. that was previously withdrawn. The claims as written are cast in product by process form, and thus, not only is sFasL not the active component as the Applicants have shown, such claims do exclude purified sFasL, as such a pure product is not produced by the claimed process.

The Examiner has rejected claims 1,2,5,6,57,58,61 and 64-66 as being anticipated by Mire-Sluis et al. The claims as written are cast in product by process form, and thus, are drawn to a composition that has manifold components, of which only some may be necessary for function. Nonetheless, the claim is not drawn to specific components as disclosed by Mire-Sluis et al. In light of the Applicants amendment of the claims to specifically track the language suggested by the Examiner, Applicants respectfully submit that this and all rejections are overcome.

Conclusion

In light of the novel and nonobvious inventive matter disclosed by the application, Applicants kindly request the Examiner withdraw the rejections of record. Accordingly, in view of the Applicants' current and previous amendments to the claims and remarks submitted herewith, allowance of all claims and passage to issue of this application respectfully is requested. Should any questions remain, the Examiner respectfully is invited to telephone the undersigned.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this Response is being sent on March 7, 2006, by to the Honorable Commissioner of Patents at the above address.

Jane Keeney